

What is claimed is:

1. Dense mineral oxide solid supports comprising
- a) a mineral oxide matrix having a pore volume which is less than 30% of the total volume of the mineral oxide matrix, and
  - b) an interactive polymer network which is rooted in pores and on the surface of the mineral oxide matrix.
2. The dense mineral oxide solid supports of Claim 1, having a density in the range of about 1.7 to 11.
3. The dense mineral oxide solid supports of Claim 2, wherein the density is in the range of about 2.1 to about 10.
4. The dense mineral oxide solid supports of Claim 1 or 2, wherein said dense mineral oxide solid supports have a particle size in the range of about 5  $\mu\text{m}$  to about 500  $\mu\text{m}$ .
5. The dense mineral oxide solid supports of Claim 4, wherein the particle size is in the range of about 10  $\mu\text{m}$  to about 100  $\mu\text{m}$ .
6. Dense mineral oxide solid supports comprising
- a) a mineral oxide matrix having a pore volume which is less than 30% of the total volume of the mineral oxide matrix, and
  - b) an interactive polymer network which is rooted in pores and on the surface of the mineral oxide matrix,
- wherein said dense mineral oxide solid supports have a density of 2.1 to 11, and a particle size of 10  $\mu\text{m}$  to 100  $\mu\text{m}$ .
7. The dense mineral oxide solid supports of Claims 1 or 6, wherein the pore volume is 5 % to 25 % of the total volume of the mineral oxide matrix.
8. The dense mineral oxide solid supports of Claim 7, wherein the pore volume is 5% to 15%.

Sub A<sup>3</sup> 9. The dense mineral oxide solid supports of Claims 1 or 6, wherein the mineral oxide matrix is comprised of titania, zirconia, yttria, ceria, hafnia, tantalia, or mixtures thereof.

5 10. The dense mineral oxide solid supports of Claims 1 or 6, wherein the interactive polymer network comprises a soluble organic polymer or a mixture of soluble organic polymers crosslinked in place with the mineral oxide matrix.

10 11. The dense mineral oxide solid supports of Claim 10, wherein the soluble organic polymer is a polysaccharide or a mixture of polysaccharides.

12. The dense mineral oxide solid supports of Claim 11, wherein the polysaccharide is selected from the group consisting of agarose, dextran, cellulose, chitosan, a glucosaminoglycan, and derivatives thereof.

15 13. The dense mineral oxide solid supports of Claim 10, wherein the soluble organic polymer is a linear soluble organic polymer selected from the group consisting of polyvinyl alcohol, a polyethyleneimine, a polyvinylamine, polyvinylpyrrolidone, a polyethyleneglycol, a polyaminoacid, a <sup>polynucleic</sup> nucleic acid, and derivatives thereof.

Sub A<sup>4</sup> 14. The dense mineral oxide solid supports of Claims 1 or 6, wherein the interactive polymer network comprises monomers, bifunctional monomers, or mixtures thereof copolymerized in place with the mineral oxide matrix.

25 15. The dense mineral oxide solid supports of Claim 14, wherein the monomers are selected from the group consisting of:

(a) aliphatic ionic, non-ionic, and reactive derivatives of acrylic, methacrylic, vinylic, and allylic compounds;

30 (b) aromatic ionic, non-ionic, and reactive derivatives of acrylic, methacrylic, vinylic, and allylic compounds;

(c) heterocyclic ionic, non-ionic, and reactive derivatives of acrylic, methacrylic, vinylic, and allylic compounds; and

(d) mixtures of any of the monomers in (a), (b) or (c).

35

16. The dense mineral oxide solid supports of Claim 15, wherein (a) is acrylamide, dimethylacrylamide, trisacryl, acrylic acid, acryloylglycine, diethylaminoethyl methacrylamide, vinylpyrrolidone, vinylsulfonic acid, allylamine, allylglycidylether, or derivatives thereof.

17. The dense mineral oxide solid supports of Claim 15, wherein (b) is vinyltoluene, phenylpropylacrylamide, trimethylaminophenylbutylmethacrylate, tritylacrylamide, or derivatives thereof.

18. The dense mineral oxide solid supports of Claim 15, wherein (c) is vinylimidazole, vinylpyrrolidone, acryloylmorpholine, or derivatives thereof.

19. The dense mineral oxide solid supports of Claim 14, wherein the bifunctional monomers are selected from the group consisting of:

- (a) bisacrylamides;
- (b) bis-methacrylamides;
- (c) bis-acrylates;
- (d) ethyleneglycol-methacrylates; and
- (e) diallyltartradiamide.

20. The dense mineral oxide solid supports of Claim 19, wherein (a) is N,N'-methylene-bis-acrylamide, N,N'-ethylene-bis-acrylamide, N,N'-hexamethylene-bis-acrylamide, or glyoxal-bis-acrylamide.

21. The dense mineral oxide solid supports of Claim 19, wherein (b) is N,N'-methylene-bis-methacrylamide, N,N'-ethylene-bis-methacrylamide, or N,N'-hexamethylene-bis-methacrylamide.

22. The dense mineral oxide solid supports of Claim 19, wherein (c) is ethyleneglycoldiacrylate, or ethyleneglycoldimethacrylate.

Sub A<sup>5</sup> 23. A method of separating a target molecule by solid phase adsorption comprising passing a sample containing said target molecule through a chromatography device loaded with a solid phase matrix comprising the dense mineral oxide solid supports of Claim 1 or Claim 6.

24. The method of Claim 23, wherein the target molecule is a biological molecule.

25. A method for separating a desired biological molecule from a sample solution containing the same comprising the steps of :

- a) loading a chromatography device with a chromatography bed comprised of dense mineral oxide solid supports comprising
  - i) a mineral oxide matrix having a pore volume which is less than 30% of the total volume of the mineral oxide matrix, and
  - ii) an interactive polymer network which is rooted in pores and on the surface of the mineral oxide matrix, wherein the interactive polymer network is functionalized to have affinity for the desired biological molecule;
- b) feeding the sample solution containing said desired biological molecule into the chromatography device, whereby the desired biological molecule is adsorbed to the dense mineral oxide solid supports;
- c) washing the chromatography device with a washing buffer and discharging undesired components and impurities of the sample solution from the chromatography device;
- d) feeding an eluting buffer into the chromatography device, wherein said eluting buffer causes the desired biological molecule to be released from the dense mineral oxide solid supports; and
- e) collecting the desired biological molecule.

26. The method of Claim 25, wherein the dense mineral oxide solid supports have a density in the range of about 2.1 to about 11.

Sub A6 > 27. The method of Claim 25 or 26, wherein said dense mineral oxide solid supports have a particle size in the range of about 5  $\mu\text{m}$  to about 500  $\mu\text{m}$ .

28. The method of Claim 27, wherein the particle size is about 10  $\mu\text{m}$  to about 100  $\mu\text{m}$ .

29. The method of Claim 25, wherein the mineral oxide matrix is comprised of titania, zirconia, yttria, ceria, hafnia, tantalia, or mixtures thereof.

30. The method of Claim 28, wherein the mineral oxide matrix is comprised of titania, zirconia, yttria, ceria, hafnia, tantalia, or mixtures thereof.

31. The method of Claim 25, wherein the interactive polymer network  
5 comprises a soluble organic polymer or a mixture of soluble organic polymers crosslinked in place with the mineral oxide matrix.

32. The method of Claim 25, wherein the interactive polymer network comprises monomers, bifunctional monomers, or mixtures thereof copolymerized in  
10 place with the mineral oxide matrix.

33. The method of Claim 25, wherein the desired biological molecule is a macromolecule.

15 34. The method of Claim 33, wherein the macromolecule is a polysaccharide, a plasmid, a nucleic acid, a polynucleotide, or a protein aggregate.

35. The method of Claim 25, wherein the desired biological molecule is a bioparticle.

20 36. The method of Claim 35, wherein the bioparticle is a virus, a viral vector, a membrane protein, or a cellular structure.

25 37. The method of Claim 25, wherein the chromatography device is a packed bed column, a fluidized bed column, or a continuous stirred tank.

38. A fluidized bed chromatography method for separating a desired biological molecule from a sample solution containing the same comprising the steps of:

5 a) loading a fluidized bed column with a chromatography bed comprised of dense mineral oxide solid supports comprising

10 i) a mineral oxide matrix having a pore volume which is less than 30% of the total volume of the mineral oxide matrix, and  
ii) an interactive polymer network which is rooted in pores and on the surface of the mineral oxide matrix, wherein the interactive polymer network is functionalized to have affinity for the desired biological molecule;

b) feeding an initial buffer into said fluidized bed column at a linear velocity which causes the dense mineral oxide solid supports to form a fluidized bed;

15 c) feeding the sample solution containing said desired biological molecule into the fluidized bed column at a linear velocity which maintains the dense mineral oxide solid supports in the fluidized bed, whereby the desired biological molecule is adsorbed to the dense mineral oxide solid supports;

20 d) washing the chromatography device with a washing buffer and discharging undesired components and impurities of the sample solution from the fluidized bed column device;

e) feeding an elution buffer into the fluidized bed column, wherein said elution buffer causes the desired biological molecule to be released from the dense mineral oxide solid supports; and

25 f) collecting the desired biological molecule eluted from the fluidized bed column.

39. The method of Claim 38, wherein the dense mineral oxide solid supports have a density in the range of about 2.1 to about 11.

30 Sub A7 40. The method of Claim 38 or 39, wherein said dense mineral oxide solid supports have a particle size in the range of about 5  $\mu\text{m}$  to about 500  $\mu\text{m}$ .

41. The method of Claim 40, wherein the particle size is about 10  $\mu\text{m}$  to about 100  $\mu\text{m}$ .

42. The method of Claim 38, wherein the mineral oxide matrix is comprised of titania, zirconia, yttria, ceria, hafnia, tantalia, or mixtures thereof.

5 43. The method of Claim 41, wherein the mineral oxide matrix is comprised of titania, zirconia, yttria, ceria, hafnia, tantalia, or mixtures thereof.

44. The method of Claim 38, wherein the interactive polymer network comprises a soluble organic polymer or a mixture of soluble organic polymers  
10 crosslinked in place with the mineral oxide matrix.

45. The method of Claim 38, wherein the interactive polymer network comprises monomers, bifunctional monomers, or mixtures thereof copolymerized in place with the mineral oxide matrix.

15 46. The method of Claim 38, wherein the desired biological molecule is a macromolecule.

20 47. The method of Claim 46, wherein the macromolecule is a polysaccharide, a plasmid, a nucleic acid, a polynucleotide, or a protein aggregate.

48. The method of Claim 38, wherein the desired biological molecule is a bioparticle.

25 49. The method of Claim 48, wherein the bioparticle is a virus, a viral vector, a membrane protein, or a cellular structure.

50. The fluidized bed chromatography method of Claim 38, wherein the linear velocity is within the range of 100 cm/hour to 3000 cm/hour.

30

51. A method for preparing dense mineral oxide solid supports which comprises:

- (a) preparing a mixture of particles of at least one mineral oxide;
- (b) forming a mineral oxide matrix from said mixture;
- 5 (c) sintering the resulting mineral oxide matrix at a high temperature which melts subparticles in the mineral oxide matrix, wherein the sintering reduces the pore volume of the mineral oxide matrix to less than 30% of the total volume of the mineral oxide matrix; and
- (d) forming an interactive polymer network rooted in the pores and on the
- 10 surface of the resulting sintered mineral oxide matrix.

52. The method of Claim 51, wherein the mineral oxide is selected from the group consisting of titania, zirconia, yttria, ceria, hafnia, tantalum, or mixtures thereof.

53. The method of Claim 51, wherein the particles of mineral oxide have a particle size of in the range of 0.1  $\mu\text{m}$  to 15  $\mu\text{m}$ .

54. The method of Claim 53, wherein the particles of mineral oxide have a particle size of 0.1  $\mu\text{m}$  to 3  $\mu\text{m}$ .

55. The method of Claim 51, wherein the dense mineral oxide solid supports have a rough surface, and wherein the particles of mineral oxide have a particle size of 3  $\mu\text{m}$  to 15  $\mu\text{m}$ .

56. The method of Claim 51, wherein the beads are formed by a sol-gel process, a spray drying process, or an emulsion-polycondensation process.

57. The method of Claim 51, wherein the interactive polymer network is comprised of monomers, bifunctional monomers, or mixtures thereof copolymerized in place with the mineral oxide matrix.

58. The method of Claim 51, wherein the interactive polymer network is comprised of a soluble organic polymer or a mixture of soluble organic polymers crosslinked in place with the mineral oxide matrix.

Add A<sup>8</sup>